'EXPERIENCE ACQUIRED' AND 'LESSONS LEARNT' SUBMITTED FOR PUBLIC CONSULTATION

Deadline for Public Consultation: 28 November 2012

UNAPECLE:

Union Nationale des Associations de Parents d'Enfants Atteints de Cancer ou de Leucémie
(French National Union of childhood cancer parents organisation)
Member of ICCCPO
International Confederation of Children Cancer Parent Organisations.

UNAPECLE was created in 2003
In 2012, UNAPECLE groups 40 associations together including 34 parent organisations
UNAPECLE obtained French National recognition

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AIMS and STRATEGY :

* Fight for sick children and their parents' rights
* Increase the accessibility to research and treatment
* Assure quality of life for children and families during and after the treatment
* Being involved in psychological assistance
* Improve integration at school (work on school integration)

The UNAPECLE is at the origin of the design of the European regulation on pediatric medicines.

This consultation was drafted by the management team

II. EXPERIENCE ACQUIRED / LESSONS LEARNT

1. A CHANGE OF CULTURE: NOWADAYS PAEDIATRIC DEVELOPMENT IS AN INTEGRAL PART OF PRODUCT DEVELOPMENT

Before the entry into force of the Paediatric Regulation many pharmaceutical companies considered the adult population as their key market. Research into the potential use of a product in the paediatric population was sidelined or not considered at all. With the obligations introduced by the Paediatric Regulation, forcing companies to screen every new (adult) product for its potential paediatric use, the situation has been turned around. Feedback from companies proves that pharmaceutical undertakings now consider paediatric development to be an integral part of the overall development of a product.

The requirement to develop and discuss with the Paediatric Committee of the European Medicines Agency a paediatric investigation plan, which normally should be submitted not later than upon completion of the human pharmaco-kinetic studies in adults, obliges companies to think early on about paediatric use so as to avoid any delays in general product development.

Consultation item No 1: Do you agree that the Paediatric Regulation has paved the way for paediatric development, making it an integral part of the overall product development of medicines in the European Union?

Yes, we agree that the Paediatric regulation has paved the way for paediatric development but too slowly for serious illness.

Companies consider now paediatric development as a regulatory obligation in the overall development of a product.
But this obligation is not an attractive challenge and the companies' behaviour is not related with parents hopes.
In fact, we know that paediatric investigation plans are not systematically submitted when pharmaco-kinetic studies are completed. In pathologies without treatment it's an important default.

In all paediatric illness, parents' faces lake of medicines to treat major or linked pathology pathologies. For example, all children (newborn, young boy or girl, adolescent) must obtain treatment for pain in all illness,

In adult cancer , all implicated companies have many strategies for developing new anticancer drugs (new pathways, ...), often targeting a specific type of cancer. Access to these new drugs or integration of children in these strategies are very difficult and rare.
In this pathology, children are still considered as small size adults. Their specificities and needs don't take place in companies' strategies.

2. HAS THE REGULATION DELIVERED IN TERMS OF OUTPUT? TOO EARLY TO JUDGE.

One of the explicit goals of the Paediatric Regulation is to reduce the off-label use of medicinal products in the paediatric population and to increase the number of products that have been researched, developed and authorised for use in children.

The main tool provided by the Regulation to achieve this result is to oblige companies to establish a paediatric investigation plan for each newly developed product or for the line extension of an already authorised product that is still under patent protection. The plan is meant to ensure — under the supervision of the Paediatric Committee — that the necessary data is generated to determine the conditions in which a medicinal product may be authorised to treat the paediatric population.

Since 2008 nearly 500 paediatric investigation plans have been approved by the European Medicines Agency[3]. However, only a minority of them has been completed. This is due to the long development cycles of medicinal products, often lasting more than a decade.

While the Paediatric Regulation has led to a certain amount of new authorisations that include paediatric indications, the regulatory instrument is recent and the data does not provide a sufficient basis for a comprehensive review. It will probably take at least a decade before the regulation can be judged in terms of its output. That said, it will always be a challenge to establish appropriate benchmarks for comparing off-label use with and without the Paediatric Regulation.

Consultation item No 2: Do you agree with the above assessment?

We don't agree with the above assessment.

Except for usual illness (large market), off label use is not regulated by Paediatric Regulation.
In oncology, the number of Paediatric Investigation Plans related with off-label used medicine is too small to be considered having any effect on the off label use in paediatric oncology. Even after a decade. (EMA/428172/2012)

3. THE PUMA CONCEPT: A DISAPPOINTMENT

The Paediatric Regulation introduced a new type of marketing authorisation, the Paediatric Use Marketing Authorisation (PUMA). As an incentive to carry out research in the potential paediatric use of off-patent medicinal products that have been authorised for adults, this marketing authorisation offers 10 years of data and market exclusivity to any new off-patent product that has been developed exclusively for use in the paediatric population. Thus, the main goal of the PUMA concept is to stimulate research in existing products. This scheme has been supported in the past by EU funding through the EU Framework Programmes for Research and Technological Development.

However, to date only one paediatric-use marketing authorisation has been granted.

Neither industry nor academic networks have responded to this opportunity as widely as the Regulation intended and aimed for. It would seem that the incentive of data and market exclusivity does not work for those products, or at least that the market opportunities in this sector are currently considered insufficient to outweigh the inherent economic risks of pharmaceutical development.

In terms of output, the PUMA concept is a disappointment.

Consultation item No 3: Do you share this view? Could you give specific reasons for the disappointing uptake of the PUMA concept? Is it likely that PUMA will become more attractive in the coming years?

The puma concept is good for all paediatric pathologies but it is unknown by academic searchers or little companies. Research on off patent medicines are mainly conducted by this kind of organisations.
For greater companies the PUMA concept, is well-known but is not used because the market opportunities are insufficient.

Information on puma concept, on EU funding through the EU framework programmes should be complete and available for all in all countries. Doctors, researchers and families need reliable information on the possibility of funding research on medications commonly used by children.
The first, in academic research will have clarification on the knowledge of off-patent medicine.
Families may require that research is directed to know the short and medium term the molecules used.
In paediatric diseases without effective treatment, the Puma concept must be extended to all statements, even if the condition of the children is not the same as adults or if it does not exist in children. You must open the puma concept to address the real needs in pediatrics and not just, as always, a transposition of indications in adults to children

In fact, the PUMA did not advance prescription drugs even in the most common drugs .Il seems that there is a great lack of information about opportunities to appeal to the pediatrician for PUMA as well as the benefits for children and their families to have medical and scientific information on drugs used to treat them and can affect all their live.
In Paediatric oncology, only the O3K project has an agreed PIP.
LOULLA, EPOC (doxorubicine) and TAIN (hydrocortisone) haven't still reached that point. [EMEA-000530-PIP02-11]

The influence of parents and their associations could become an asset for the PUMA but they are mainly driven by physicians to support new developing drugs.

4. WAITING QUEUES? NO EVIDENCE OF DELAYS IN ADULT APPLICATIONS

Within the regulatory framework provided by the Paediatric Regulation, the need to comply with a paediatric investigation plan is subject to the commitment that the requirement for study data in the paediatric population does not block or delay the authorisation of medicinal products for other populations. The main instrument in this regard is the possibility to defer the initiation or completion of some or all of the measures contained in a paediatric investigation plan.

Experience has shown that deferral is a widely used instrument and that in general no delay in the processing of 'adult' applications is encountered. Problems may occur, but only in exceptional cases, especially if a company is late in discussing its planned paediatric research programme with the Agency and the Paediatric Committee. This is also one of the main reasons why the Paediatric Regulation requires companies to submit the paediatric investigation plan no later than upon completion of the human pharmaco-kinetic studies in adults.

Consultation item No 4: Do you agree that, generally speaking, the paediatric obligations have no impact on timelines in adult development, as there is no evidence for delays in marketing authorisation applications for reasons of compliance with the paediatric obligation? If you feel that there is an impact, practical examples would be appreciated.

To our knowledge and in childhood cancer, the paediatric obligations did not have impact on timelines in adult development.

5. MISSING THE POINT? PAEDIATRIC DEVELOPMENT IS DEPENDENT ON ADULT DEVELOPMENT, NOT PAEDIATRIC NEEDS

The starting point for the majority of paediatric investigation plans is an ongoing research and development programme for a medicinal product for the adult population. An intrinsic consequence of this approach is that the conditions those products primarily target are adult conditions. They are developed in areas where there is a need (or a market) in the adult population. That need in the older population does not necessarily correspond to the paediatric population's need.

While the Paediatric Regulation ensures that these future products are screened for their potential use in children, its regulatory framework cannot guarantee that products become swiftly available in all paediatric conditions. Rather, progress in terms of authorised products for use in children depends to a considerable extent on a company's product strategy with respect to the adult population.

It might be argued that this is perfectly normal, as medicinal development is company driven. Moreover, as in the past, companies will continue to develop products specifically for children. The Orphan Regulation also provides incentives for the development of medicines in areas of unmet therapeutic needs.

It is not the purpose of the Paediatric Regulation to replace an established system of medicinal product development by a new regulatory system. It aims to ensure that every innovation and every new product is screened for its potential use in children so that over time there will be a significant increase in the number of products for which specific paediatric data is available.

Consultation item No 5: Do you have any comments on the above?

The needs of children are not those of adults.

There are two categories of needs for children:

- drugs that treat the same disease in children and adults and for which much progress remains to be done in taste, formulation (galenic form) and so on

- drugs that are specific to children either because their disease is very different from the adult, either because it does not exist in adults.

In 2 cases, the strategies of development are not identical and must be decided by industrials.

However, in the case of pediatric drug needs are urgent and essential, applications should be able to come to the EMA. A commission should be able to identify these specific unmet needs and also determine the pediatric indications that have no link with adult indications but that could be the development of drugs that would cure children.

6. THE BURDEN/REWARD RATIO — A BALANCED APPROACH?

There can be no doubt that the Paediatric Regulation places a considerable additional burden on pharmaceutical companies with its obligations regarding research in products for use in children. However, this approach was adopted because market forces alone had proven insufficient to stimulate adequate research.

At the same time the Paediatric Regulation introduced a number of incentives intended to offset the additional burden, at least partially. One of the main incentives is the 6-month extension of the Supplementary Protection Certificate. While it is too early to assess the economic impact of the rewards — a topic which will be covered in a second Commission report due in 2017 (Article 50(3) of the Paediatric Regulation) — the European Medicines Agency and its Paediatric Committee have made acknowledged efforts to simplify the regulatory process wherever possible and within the limits of the regulatory framework. In addition, information is published systematically and Questions and Answers documents are updated for frequently asked questions.

Consultation item No 6: Do you agree with the above?

Our associations can only see the heavy process, but are not directly involved.

However, it appears important to us to maintain a high level of demand on pharmaceutical companies to assure safety for children. We do not want to see perform unnecessary tests or badly made. Procedures must be alleviated but never compromising on safety and welfare of children.

An important point in pediatric oncology is that the insurance companies consider any clinical trial comparing an off label prescription with a new drug as twice as risky as any pediatric research. In addition to the fact that (due to the toxicity of most of this drugs) the risk of a single trial is highly evaluated. The insurance fee are therefore very high and this burden may never be covered by the potential reward.

The insurance fees should be partly funded by EU in some cases to equilibrate this ratio.

7. ARTICLES 45/46: THE HIDDEN GEM OF THE PAEDIATRIC REGULATION

To provide better information on the use of medicinal products in the paediatric population, Article 45 of the Paediatric Regulation requires companies holding data on the safety or efficacy of authorised products in the paediatric population to submit those studies to the competent authorities. In this way the data can be assessed and, where appropriate, the authorised product information can be amended. Additionally, Article 46 of the Regulation requires companies to submit newly generated paediatric data.

Since 2008 more than 18.000 study reports on roughly 2 200 medicinal products have been submitted to the competent authorities, revealing the large amount of existing paediatric information available at company level.

These study reports have been, and continue to be, assessed by the competent authorities thanks to an impressive work-sharing project. This has led to the publication of assessment reports covering more than 140 active substances and, in a considerable number of cases, to recommendations for changes to the summary of product characteristics of authorised products[4].

While competent authorities are empowered to vary marketing authorisations as a result of the assessment, marketing authorisation holders have shown little interest in updating the summary of product characteristics and product information on a voluntary basis[5].

Nevertheless, the requirements of Articles 45 and 46 have provided an efficient and appropriate instrument for collecting existing paediatric studies and reaping the benefits.

Consultation item No 7: Do you agree that Articles 45/46 have proved to be an efficient and successful tool for gathering and compiling existing paediatric data and making it available to the competent authorities and subsequently, via databases, to the interested public?

Articles 45 and 46 were desired by parents' associations in order not to increase testing and have important and reliable information on medicines given to children.

We have no doubt that informations are transmitted and analyzed but parents and associations do not have access.

We suggest that fact sheets must be established for the public for each drug . This work is starting within the ENCCA EU-project but mainly for improving the long term monitoring of patients treated with high-toxicity drugs and not based on an existing database.

Those data should be summarized and published in all EU-languages on a dedicated website as soon as possible.

8. LOST IN INFORMATION: HEALTHCARE PROFESSIONALS NOT AS RECEPTIVE AS EXPECTED

Some studies published in the medical literature suggest a lack of recognition by general practitioners of the actual amount of off-label prescribing to children[6]. It is argued that paediatricians are not always aware of the off-label status of the products they prescribe or that they do not consider that some of the frequently used medicines for children are in fact not authorised for use in this age group.

Moreover, it is claimed that the prescribing habits of practitioners are often strongly influenced by personal experience rather than by evidence-based information.

Such observations may point to a significant hurdle to achieving the goal of the Paediatric Regulation, that is to reduce the amount of off-label prescribing. If the instrument is to be a success, it is necessary not only that the data on the use of a specific product in the paediatric population is assembled, but that this data is then also appropriately communicated to, and used by, paediatricians in their day-to-day practice for the benefit of their patients.

National competent authorities as well as healthcare professional organisations would seem to be specifically qualified to consider appropriate ways of ensuring an adequate flow of information. On their own, the regulatory instruments provided by the Paediatric Regulation seem to be reaching their limits here.

Consultation item No 8: Do you agree that healthcare professionals may not always be as receptive to new scientific information on the use of particular products in children as might be expected? Do you agree that this problem has to be addressed primarily at national level? How could healthcare professionals be more interested and engage in paediatric clinical research?

The pediatricians in oncology are highly aware that the drugs they prescribe are most of the time not authorized for use in an age group. Other health professionals are less informed.
This is why the paediatric regulation was designed.

But the National Level (especially in France where the Health Authorities has been weakened by recent affairs) may not be relevant to address the problem of off label prescription.
A European definition of a “usual off label prescription list” (maybe for each pathology) could ease the beginning of self-regulation and National comparisons

More studies on the efficacy and safety of the products can be used to collect information on pharmacovigilance, long-term effects or troublesome side effects or having influence on the development of children. All this information is important for parents responsible for the lives and the future of their children and effective organization in the field of information must be quickly put in place for all stakeholders dealing with sick children: caregivers, parents, health authorities so on

9. CLINICAL TRIALS WITH CHILDREN: NO SPECIFIC PROBLEMS DETECTED

In order to compile additional data on the use of products in children, medicinal products need to be tested more frequently in the paediatric population. It is therefore quite likely that the Paediatric Regulation will lead to more clinical trials in that population.

The figures in the EudraCT database[7] do not yet show an increase in paediatric trials. The number of paediatric trials remained stable between 2006 and 2011, hovering, with some ups and downs, around an average of 350 trials per year. It should be pointed out, however, that EudraCT is limited to clinical trials that commence in the European Union and that while the number of paediatric trials remained stable, the number of clinical trials in all populations decreased between 2007 and 2011.

It is also generally accepted that the aims of the Regulation should be achieved without subjecting the paediatric population to unnecessary clinical trials. There is therefore a continuous effort to explore alternative means, e.g. the use of extrapolation of efficacy[8].

Especially sensitive are the youngest paediatric age subsets, including neonates. It will be a continuous challenge to balance the therapeutic needs of those age groups against their specific vulnerability when reflecting and deciding on the appropriateness of specific clinical trials or about the specific settings of any study in that population (subsets).

Another challenge is how to avoid duplicating trials for different paediatric investigation plans from different applicants. Companies embarking on product development in similar areas may be required by an agreed paediatric investigation plan to conduct studies within similar settings. While this seems to be a way of avoiding discriminatory treatment between different companies, it may potentially lead to a duplication of trials which from a scientific point of view would be unnecessary.
Here, the key to avoiding such unnecessary trials is transparency with regard to ongoing and completed trials.

Consultation item No 9: Do you have any comments on developments in clinical trials with children following the adoption of the Regulation and in view of the above description?

French agency also notes stability in paediatric tests or a slight decrease.
We are not too worried about this because there are many elements that can come into play. We prefer well organized and targeted testing rather than uncontrolled increase unchecked.

Sometimes knowledge is not sufficient even if the parents are very impatient. But when there is ample evidence of the benefits of a drug for a disease or care for children, no attempt was made in this area then aid must facilitate this work so that families do not seek not any solution in all countries and with considerable investments.

10. UNNECESSARY EFFORTS? NON-COMPLETED PAEDIATRIC INVESTIGATION PLANS

The Paediatric Regulation requires companies to submit paediatric investigation plans at an early stage of product development (end of 'phase I'). However, research in some active substances which have completed phase I may be discontinued at later stages, if further studies fail to show potential with respect to the safety and efficacy of the product. For every successful authorised medicinal product there are many that fail to make the finishing line.
Hence, not all approved paediatric investigation plans will be completed, as companies may decide to stop the corresponding adult development. It is too early for reliable statistics showing the ratio between completed and non-completed paediatric investigation plans, but in the current context it is an unavoidable fact that not all approved plans will eventually result in an approved medicine with a paediatric indication.
In terms of output, this leads to some unnecessary efforts involving the compilation and screening of paediatric investigation plans. On the other hand, early submission of and agreement to the paediatric investigation programme is necessary for the paediatric development to fit smoothly into the overall product development.

Consultation item No 10: Do you have any comments on this point?

An important point in oncology is the extrapolation to children of the improvements in widely represented adult cancers. Both in terms of curing improvement and of potential late adverse effects.
What we feel is that most of the industrials tend to avoid Pediatric Investigation Plans because of the burden in money and time.

If there is some evidence that the active molecule has an interest in children, we must find a way to negotiate a pip and have a little extra time to discuss the effectiveness and product interest.

We could imagine a specific network of Academic researchers or not, interested in the development of innovative molecule and comprising scientists, physicians and parent associations while members are formed in research.

11. SOPHISTICATED FRAMEWORK OF EXPERTISE ACHIEVED

The Paediatric Regulation has led to the establishment of a comprehensive network of expertise within the European Union in paediatric matters, with the Paediatric Committee at the forefront bringing together a high level of expertise and competence in the development and assessment of all aspects of medicinal products to treat the paediatric population. Additionally, the European Network for Paediatric Research at the EMA (Enpr-EMA) was established in 2009. This is a unique European network of national and European networks, investigators and centres with specific expertise in the design and conduct of studies in the paediatric population.
The adoption of the Paediatric Regulation has acted as a form of catalyst, gearing up and coordinating expertise and bringing the topic of medicines for children to the fore.

Consultation item No 11: Do you agree that the Paediatric Regulation has contributed substantially to the establishment of a comprehensive framework of paediatric expertise in the European Union?

Yes we think that . However, this network of expertise is not sufficiently exploited.

The work in progress within any disease specific EU-project (such as ENCCA) should be more connected with others to lead to a deeper and wider expertise network.

It should focus on the most critical needs of children and provide more space for parents who are now experts on their child's illness. Like in Pedco at the Ema, representatives of parents' associations are essential in decision-making bodies to describe the real needs of sick children.

It may also intervene in areas where there is no treatment and in which industry seem to be afraid to invest

12. ANY OTHER ISSUE?

Consultation item No 12: Overall, does the implementation of the Regulation reflect your initial understanding/expectations of this piece of legislation? If not, please precise your views. Are there any obvious gaps with an impact on paediatric public health needs?

To enforce this regulation and encourage even more pharmaceutical companies to study existing and new drugs for children it is essential to pool all existing knowledge on developments in children. We must build an international network in order not to increase testing.

The information is an essential element for all settlement and not enough emphasis on this point. This information must be accessible and understood by all.

On this specific topic (share and spread information), the parents and patients associations should be of great help and therefore more directly involved.

An other point, is the poor interest that French pediatric oncologists seem to have in EU-regulation. EU is not seen as an effective tool to improve the research activity but more a limiting factor thru the clinical trials regulation.

At the opposite, as parents of sick childrens we find it appropriate and normal to have both a brake and an accelerator to drive the development of drugs for our childrens

Of time. European children sick today may not be tomorrow ill adults and Europe is responsible for its future actors.

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